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Immunopathogenesis pathways of primary immune thrombocytopenia: a comprehensive overview

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anti-platelet antibodies; CTLs; platelets apoptosis; TFH cells; megakaryocytes; B cells

ABSTRACT

Primary immune thrombocytopenia (ITP) is an autoimmune disorder characterized by both the destruction and impaired production of platelets. Mucocutaneous bleeding is the predominant symptom in patients with severely reduced platelet counts. The pathogenesis of ITP involves complex immune mechanisms initiated by aberrant T cell responses and the action of splenic T follicular helper cells, which activate autoreactive B cells. These B cells produce anti-platelet autoantibodies that promote platelet phagocytosis by macrophages; the primary antigen-presenting cells in ITP. Additionally, enhanced cytotoxic T-cell activity induces platelet apoptosis, further contributing to thrombocytopenia. Immune-mediated targeting of megakaryocytes, along with reduced levels of thrombopoietin (the principal growth factor for megakaryocyte maturation) results in dysfunctional bone marrow platelet production. This review outlines the immune mechanisms driving ITP and elucidates the roles of immune cells in both platelet destruction and impaired production.

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1. Introduction

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder affecting both adults and children; it presents with haematological manifestations characterized by bleeding and a platelet count of less than 100×10^9/L, due to underlying mechanisms that increase platelet clearance and impair megakaryopoiesis and thrombopoiesis. ITP is categorized into primary and secondary forms. Approximately 80% of newly diagnosed adult cases are primary ITP, with no identifiable predisposing factors. However, autoimmune conditions such as Graves' disease, Hashimoto's thyroiditis, autoimmune haemolytic anaemia, antiphospholipid syndrome, rheumatoid arthritis, and

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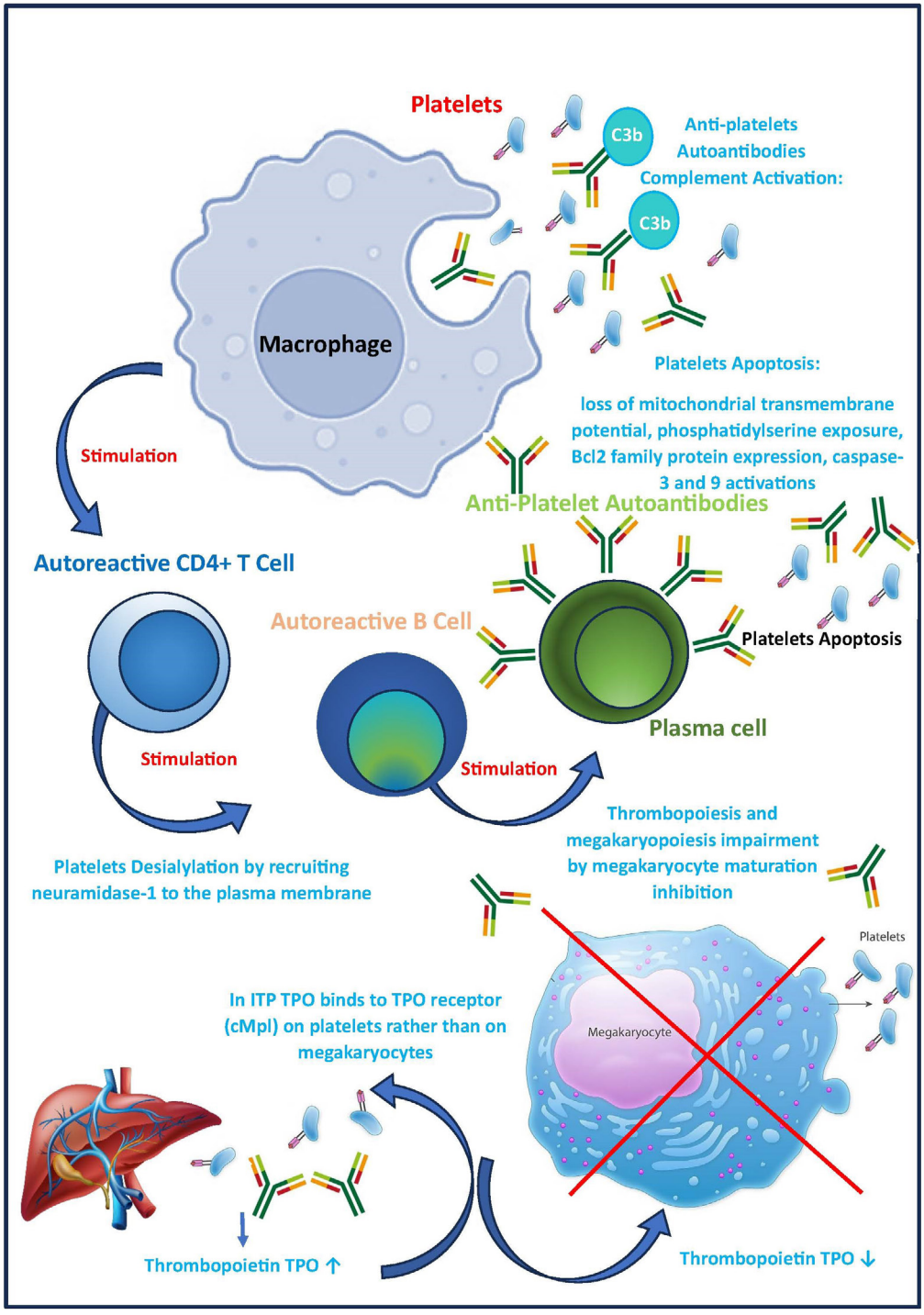

Figure 1. *Overview of the immunopathogenic mechanisms underlying primary immune thrombocytopenia (ITP). Anti-platelet autoantigens lead to platelet destruction and impairment of their production via a number of pathways (including complement activation, platelet apoptosis, platelet desialylation, and inhibition of the megakaryocyte maturation). Abbreviations used: C3b; complement C3b protein; TPO, thrombopoietin.*

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systemic lupus erythematosus may act as risk factors or co-occur with secondary ITP. Secondary ITP can also be triggered by infections, malignancies, or certain medications[1]. A diagnosis of primary ITP is established after excluding other causes of thrombocytopenia typically associated with secondary ITP[2]. This review aims at elucidating the immunopathogenic pathways of primary ITP, focusing on the roles of autoantibodies and immune cells in disease development, in order to better inform optimized therapeutic strategies and improve patient outcomes.

2. Mechanisms of platelet destruction and megakaryopoiesis dysregulation

2.1. Autoantibody-related mechanisms

A dysregulated immune response and the loss of tolerance to platelet surface autoantigens lead to the formation of autoantibodies, which play multiple roles in the pathophysiology of primary ITP. These autoantibodies, predominantly IgG, target platelet surface glycoproteins. Antibody-coated platelets are cleared from circulation *via* a macrophage-mediated phagocytosis. Macrophages serve a dual role, as effector cells and as principal antigen-presenting cells, thereby stimulating autoreactive $CD4^+$ T cells (including follicular helper T cells; TFHs), which in turn activate autoreactive B cells in order to differentiate them into antibody-producing plasma cells[2].

Autoantibodies can also activate the complement system, leading to C3b deposition on antibody-coated platelets. This enhances their phagocytosis by splenic macrophages. Complement involvement is observed in approximately half of the ITP cases and is associated with autoantibody specificity; in fact, anti-GPIIb/IIIa antibodies are more likely to activate complement than anti-GPIb/IX antibodies[3].

Platelet apoptosis represents another pathogenic mechanism triggered by anti-platelet autoantibodies; it involves a mitochondrial depolarization, phosphatidylserine exposure, altered expression of Bcl-2 family proteins, and an activation of caspases (particularly caspase-3 and -9), which are significantly implicated in ITP-associated platelet apoptosis[2].

Autoantibodies also impair thrombopoiesis and megakaryopoiesis by inhibiting megakaryocyte maturation, resulting in decreased platelet production[2]. An additional pathway of platelet destruction involves antibody-mediated desialylation. In the latter case, autoantibodies recruit neuraminidase-1 to the platelet membrane, thereby accelerating the removal of sialic acid residues. Desialylated platelets are then recognized by the Ashwell-Morell receptor on hepatocytes, leading to their clearance and the induction of thrombopoietin (TPO) production; a key growth factor for megakaryocytes[3]. In ITP, TPO levels are inappropriately regulated. TPO activates megakaryocytes *via* its receptor, c-Mpl, which is also expressed on platelets. The circulating platelet pool influences TPO availability (Figure 1). Under normal conditions, thrombocytopenia increases free TPO, thereby enhancing platelet production. Conversely, thrombocytosis depletes free TPO by increasing platelet binding. In ITP, circulating platelet levels may appear normal, yet platelets are rapidly destroyed, binding excessive TPO and reducing its bioavailability. Consequently, TPO concentrations in ITP patients are lower than in those with aplastic anaemia, despite similar platelet counts[4].

2.2 Immune cell-related mechanisms

The immunopathogenesis of primary ITP involves several immune cell types, including $CD4^+$ T cells, antigen-presenting cells (macrophages and dendritic cells), B cells, plasma cells, TFHs, cytotoxic T lymphocytes (CTLs), Th17 cells, and regulatory T cells (Tregs). The latter play a crucial role in maintaining immune tolerance by modulating T and B cell-mediated autoimmunity and by inducing a tolerogenic phenotype through interactions with antigen-presenting cells. A loss of peripheral tolerance arises from impaired Treg activity – whether due to reduced generation or altered function – and is associated with disease severity. This breakdown of self-tolerance contributes to T-cell dysregulation and initiates aberrant antigen presentation. Consequently, abnormal Th cell production occurs, along with Th-cell anergy and an imbalance in the Th1/

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Th2 ratio, which inversely correlates with disease severity[5].

Antigen-presenting cells (APCs) present platelet autoantigens to autoreactive $CD4^+$ T cells, triggering a cascade that culminates in the production of anti-platelet autoantibodies by autoreactive B cells (that aberrantly differentiate into plasma cells) (Figure 1). These autoantibodies target platelets and megakaryocytes, thereby promoting their dysfunction and clearance in the spleen and liver[2].

Dendritic cells contribute to the immune activation as monocyte-derived APCs capable of phagocytosing apoptotic platelets and stimulating T cells. They possess tolerogenic properties and are instrumental in converting naïve T cells into Tregs, while also guiding T-cell polarization toward a Th2 phenotype[5]. In primary ITP, dendritic cells exhibit increased expression of co-stimulatory molecules (CD80 and CD86) and elevated production of interleukin-12 (IL-12); changes correlated with Treg deficiency and heightened pathogenic T cell activation[6].

TFHs are central to ITP pathogenesis; they express the surface receptor CD154 and are major producers of IL-21, thereby facilitating autoreactive B cell differentiation and promoting anti-platelet antibody production[7]. At the same time, CTLs also play a significant role. $CD8^+$ CTLs mediate platelet destruction through direct, contact-dependent cytotoxicity (likely occurring in the spleen). CTLs are also recruited to the bone marrow, where they target megakaryocytes. Evidence supports that both humoral and T cell-mediated autoimmunity contribute to megakaryocyte dysfunction and destruction in patients with ITP, representing an additional pathogenic mechanism alongside peripheral platelet clearance[8].

Finally, Th17 cells contribute to autoimmunity by secreting proinflammatory cytokines, notably IL-17, which is found at elevated levels in ITP patients (when compared to those of healthy individuals). IL-17 promotes the expression of other inflammatory mediators (including IL-6, transforming growth factor beta, matrix metalloproteinases, and intracellular adhesion molecule-1) across various cell types (such as bone marrow stromal cells), thereby sustaining the inflammatory cytokine milieu that is characteristic of ITP[9].

3. Conclusion

Multiple immunological pathways contribute to platelet destruction and impaired production in ITP, driven by a loss of self-tolerance to platelet surface autoantigens. Understanding these mechanisms is essential for the development of targeted immunotherapies aimed at improving outcomes in patients with primary immune thrombocytopenia.

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Conflicts of interest

None exist.

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